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Is prostate-specific antigen density superior than prostate-specific antigen kinetics and prostate volume in predicting clinically insignificant prostate cancer?

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ABSTRACT

Objectives: In this study, we aimed to evaluate the parameters that could predict clinically insignificant prostate cancer (ciPCa) in men who underwent transrectal ultrasound (TRUS)-guided prostate biopsy.

Methods: Data of patients who underwent transrectal prostate biopsy between January 2015 and November 2019 were examined retrospectively. Free/total PSA ratio (fPSA%), serum total and free prostate-specific antigen (PSA) levels, prostate volumes (PV) measured by ultrasonography, and PSA density (PSAD) values of the patients before biopsy were recorded. ciPCa patients were defined as patients with Gleason scores ≤6 and clinical stage ≤T2a (Group 1). The remaining patients (Gleason score >6 and clinical stage >T2a) were included in Group 2 (clinical significant prostate cancer (csPCa). The parameters examined before biopsy were compared between groups.

Results: After performing the exclusion criteria, the study counts in 168 patients with the current data of total/free PSA levels, age, PV calculated by TRUS, rectal examination findings, and pathology reports. Group 1 consisted of 115 patients and Group 2 consisted of 53 patients. In the univariate analysis, PV, total PSA and PSAD were found significantly different between groups, while age, free PSA, and fPSA% showed no significant difference between the two groups. According to the results of the multivariate analysis, the independent predictor of ciPCa was determined to be PSAD while total PSA and PV were not independent predictors.

Conclusion: PSAD was found to be superior to other PSA kinetics in predicting ciPCa.

Keywords: Prostate-specific antigen, prostate cancer, prostate-specific antigen density, prostate volume

Prostate cancer (PCa) is the most commonly diagnosed cancer in men after lung cancer and is a leading cause of cancer-related deaths. In 2020, 1.4 million people were diagnosed, accounting for 15% of all cancers [1]. Prostate-specific antigen (PSA) screening test is widely used all over the world for early diagnosis of the disease. However, PSA causes difficulties in the diagnosis of prostate cancer. Because the specificity of PSA is low. Therefore, various studies have been conducted to get better cancer prediction using different PSA kinetics such as age-referenced PSA, Free/total PSA ratio (fPSA%), PSA density (PSAD), and PSA velocity [2-4]. In most studies, these diagnostic methods have been used to pre-

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dict prostate cancer patients. Their effectiveness in distinguishing clinically significant cancers has been less studied. However, in the diagnosis of PCa, the main goal is to distinguish between clinically significant prostate cancer (csPCa) and clinically insignificant prostate cancer (ciPCa) to reduce overdiagnosis. On the other hand, adenocarcinoma must be seen in prostate biopsy samples for a definitive diagnosis, but the cancer is detected in only 25% of all biopsies [5]. In addition, various complications ranging from simple hematuria to sepsis may occur as a result of prostate biopsy [6].

Therefore, in this study, we aimed to investigate the success of PSA kinetics and PV in forecasting ciPCa in order to decrease redundant biopsies and overdiagnosis. In addition, we aimed to determine the proper cut-off values of the parameters that would be statistically significant in predicting ciPCa. The primary outcome of the study is to investigate the role of PSA kinetics in predicting ciPCa patients, and the secondary outcome is to determine the cut-off values of these parameters in predicting ciPCa.

METHODS

For the study, ethics committee approval was obtained from the University of Health Sciences Bursa Yuksek Ihtisas Training and Research Hospital ethics committee, dated 29.01.2020 and numbered 2020/01-08. The data of 1901 men who underwent transrectal ultrasonography-guided prostate biopsy patients between 40-80 years in a urology outpatient clinic between February 2015 and November 2019 were retrospectively scanned. Indications for prostate biopsy was serum PSA levels >2.5 ng/mL and abnormal digital rectal examination (DRE). Patients with PSA levels >10 ng/mL, patients receiving 5-alpha-reductase inhibitor therapy, and patients with a history of any invasive treatment for benign prostatic obstruction were excluded from the study. Additionally, patients who had undergone an endoscopic procedure, biopsy, urinary tract infection, and urinary retention within the last month were also excluded from the study.

Serum PSA levels were obtained in ng/mL using chemiluminescent microparticle immunoassay (CMIA) before any prostate manipulation. fPSA% was calculated by free PSA/total PSA×100. The patients' PV was calculated by measuring three dimensions of the prostate (PV = length×width×length×0.52). PSAD was obtained by dividing the serum total PSA level by the prostate volume measured by ultrasonography. The patients included in the study are those who have had at least 12 core biopsies. Patients who underwent multiple biopsies were included in the study according to their last biopsy results, PSA levels, and prostate volumes from the last biopsy period.

Clinically insignificant prostate cancer (low-risk patients) was defined as Gleason score ≤6 and clinical stage ≤T2a. Patients who met both ciPCa criteria were included in Group 1, and the remaining prostate cancer patients were included in Group 2. Between groups, PSAD and prostate volume, age, total PSA, and free PSA were compared.

Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 software (SPSS, Inc., Chicago, IL, USA). Shapiro-Wilk test was used to interpret the suitability of the data to the normal distribution curve. Continuous and categorical data were compared using the Mann-Whitney U test and Chi-square test, respectively. Logistic regression multivariate analysis was performed to identify independent predictive factors. The receiver operating characteristic (ROC) curve was used to evaluate and compare the effectiveness of PSAD, prostate volume, and total PSA. $P<0.05$ value was considered statistically significant.

RESULTS

A total of 168 patients with available data were included in the study. ciPCa consisted of 115 patients and csPCa consisted of 53 patients. Table 1 includes the baseline data of the groups and the comparison of the groups in terms of these parameters.

In univariate analysis, PV was found to be significantly higher and total PSA and PSAD were significantly lower in Group 1 compared to Group 2. Age, free PSA, and fPSA% did not differ significantly between the two groups (Table 1). In ROC analysis, the sequence of AUCs was determined as total PSAD>PV> total PSA (Table 2).

Table 1. Clinical characteristics of the patients

Parameters	Total Cohort (n=168)	Group 1 (n=115)	Group 2 (n=53)	Group 1 vs. Group 2 P value
Age (years)				
Mean±SD	64±7.19	64.59±7.06	65.81±7.22	0.168
Median (min-max)	65 (44-81)	65 (44-81)	66 (48-79)	
Total PSA (ng/mL)				
Mean±SD	6.35±1.96	6.08±1.96	7.09±1.68	**0.004**
Median (min-max)	6.32 (1.28-9.89)	5.97 (1.28-9.89)	7.19 (3.90-9.86)	
Free PSA (ng/mL)				
Mean±SD	0.34±0.82	1.26±0.63	1.52±1.11	0.222
Median (min-max)	1.23 (0.19-6.70)	1.17 (0.19-3.32)	1.27 (0.36-6.70)	
Free/Total PSA				
Mean±SD	0.21±0.11	0.21±0.09	0.22±0.14	0.688
Median (min-max)	0.19 (0.05-0.89)	0.18 (0.05-0.53)	0.19 (0.05-0.84)	
Prostate volume (cc)				
Mean±SD	50.32±29.77	63.31±28.23	44.31±32.68	**0.003**
Median (min-max)	44 (10-206)	46 (15-206)	33 (10-190)	
PSAD (ng/mL/cc)				
Mean±SD	0.166±0.103	0.14±0.08	0.22±0.12	**<0.001**
Median (min-max)	0.13 (0.02-0.63)	0.11 (0.02-0.44)	0.20 (0.02-0.63)	

PSAD=Prostate-specific antigen density, PSA= Prostate-specific antigen, SD=standard deviation, min=minimum, max=maximum, Group 1=clinically insignificant prostate cancer, Group 2= clinically significant prostate cancer

Multivariate analysis was applied to PSAD, PV, and total PSA, which were found to be significant in univariate analysis. According to the multivariate analysis results, the independent predictor of ciPCa was determined to be PSAD, while total PSA and PV were not independent predictors (Table 3). Cutoff values for PSAD, total PSA, and PV were determined for the prediction of ciPCa. ROC analysis revealed a cut-off value of 0.157 ng/mL/cc with 69.8% sensitivity and 69.6% specificity for PSAD, and 6.31 ng/mL with 64.2% sensitivity and 55 specificity for total PSA % and the cut-off value for PV is 35.5 cc, with a sensitivity of 77.2% and a specificity of 55% (Fig. 1). The numbers and percentages of groups, and the p values when patients are divided according to these cut-off values, are shown in Table 4. The distribution of Group 1 patients into quartiles when grouped by PSAD, total PSA, and PV is shown in Table 5.

Table 2. The AUCs for total PSA, prostate volume, and PSAD in predicting clinically significant prostate cancer.

	AUC	%95 CI	P value
Total PSA	0.639	0.552-0.725	**0.004**
Prostate volume	0.641	0.547-0.734	**0.003**
PSAD	0.713	0.625-0.801	**<0.001**

PSAD=Prostate-specific antigen density, PSA= Prostate-specific antigen, AUC=Area under the curve

Table 3. Multivariate analysis of independent predictors of clinically significant prostate cancer.

	Odds ratio	95% Confient interval	P value
Total PSA	1.044	0.834-1.307	0.708
Prostate volume	1.015	0.998-1.032	0.094
PSAD	50.792	103.4-24930132.4	**0.001**

PSAD=Prostate-specific antigen density, PSA= Prostate-specific antigen

DISCUSSION

Since PSA is insufficient to predict prostate cancer, both new laboratory and new imaging methods are being developed to predict ciPCa [7, 8]. These methods aim to reduce overdiagnosis and subsequent overtreatment. The desired features of these methods are that they are cheap, easily accessible, and non-invasive. In our study, we investigated whether PSAD, prostate volume, total PSA, and fPSA%, which can be measured in peripheral blood and measured on USG, have a place in the prediction of ciPCa. According to our study results, we concluded that among PSA derivatives, only PSAD can predict ciPCa.

The search for more specific and sensitive markers continues to predict ciPCa in the patient group with PSA values in 4-10 ng/mL. Since it is known that the PSA level increases as the prostate volume increases, Benson *et al*. in their article published in 1992, they wrote that the ratio of serum PSA level to prostate volume could facilitate the detection of PCa. In this study, where it was first described, PCa and BPH patients

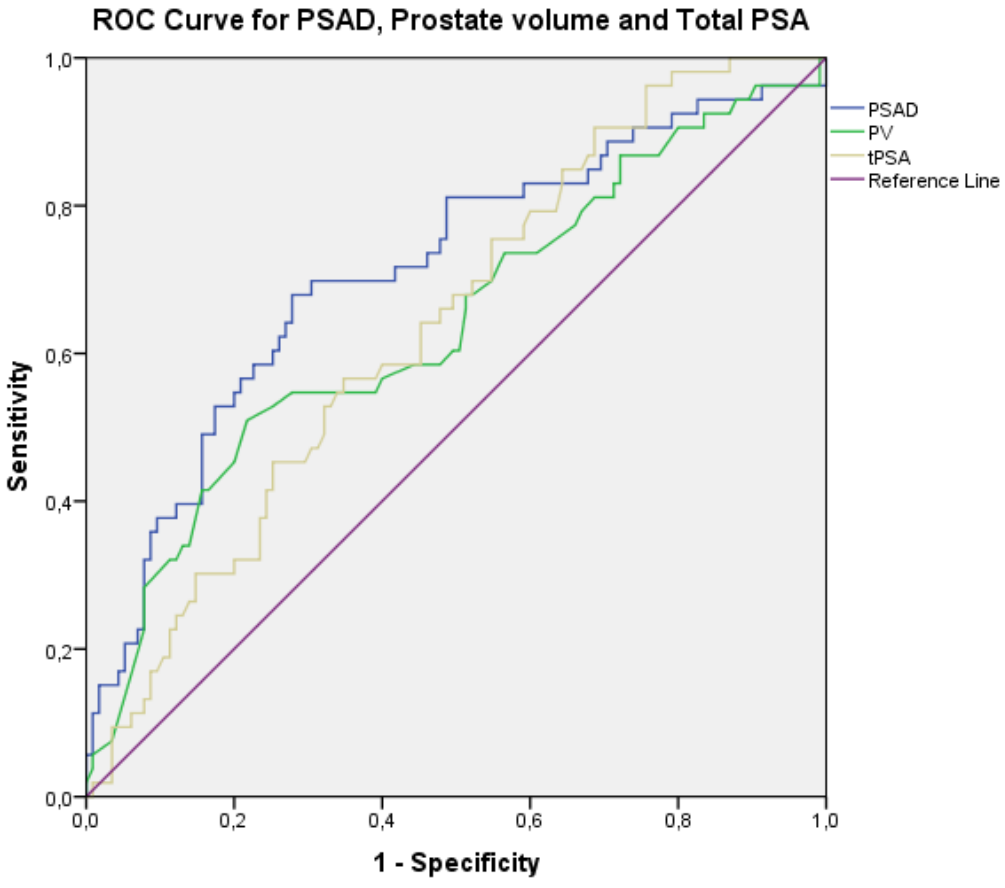

Fig. 1. ROC analysis for PSAD, total PSA and PV for the prediction of ciPCa. PSAD=Prostate-specific antigen density, PSA= Prostate-specific antigen, PV= Prostate volume, ciPCa= clinically insignificant prostate cancer.

Tablo 4. Comparison of patient's age, total PSA, free PSA, free/total PSA ratio, prostate volume, and clinically significant PCa according to the cut-off value of PSAD.

Parameters	PSAD		P value
	<0.157	>0.157	
Number of pateints			
(n=168)	95	73	
(100%)	(%56.5)	(%43.5)	
Age (years)			0.953
Mean±SD	65.15±6.37	64.75±8.01	
Median (min-max)	65 (47-78)	66 (44-81)	
Total PSA (ng/mL)			
Mean±SD	5.72±1.86	7.25±1.66	**<0.001**
Median (min-max)	5.80 (1.28-9.89)	7.52 (3.78-9.86)	
Free PSA (ng/mL)			
Mean±SD	1.34±0.66	1.35±1.01	0.315
Median (min-max)	1.28 (0.19-3.22)	1.07 (0.36-6.70)	
Free/Total PSA			
Mean±SD	0.23±0.09	0.19±0.12	**<0.001**
Median (min-max)	0.22 (0.07-0.56)	0.16 (0.05-0.84)	
PV (cc)			
Mean±SD	65.73±31.02	30.59±10.49	**<0.001**
Median (min-max)	60 (24-206)	31 (10-58)	
Group			
Group 1 (ciPCa)	79 (%83.1)	36 (%49.3)	**<0.001**
Group 2 (csPCa)	16 (%16.9)	37 (%50.7)	

PSAD=Prostate-specific antigen density, PSA= Prostate-specific antigen, PV=Prostate volume, PCa=Prostate Cancer, csPCa=clinically significant prostate cancer, ciPCa=clinically insignificant prostate cancer, SD=standard deviation, min=minimum, max=maximum

were compared and a statistically significant higher rate was found in the PCa group [9]. PSAD is obtained by dividing the PSA value by the prostate volume [1]. As this rate increases, the probability of having csPCa increases.

Many studies in the literature have shown a relationship between PSAD and PCa. In the study of Yusim *et al*. [10], 992 patients were included. They showed that PSAD had a role in predicting both PCa and csPCa. They concluded that patients with PSAD value below 0.09 ng/mL were less likely to have csPCa [10]. Omri *et al*. [11] included 364 patients to the study and, they divided the patients into 3 groups according to their prostate volume (<50 cc, 50-75 cc, >75 cc). According to the results, PSAD was correlated with csPCa in medium and low-sized prostates, but not in large-sized prostates [11]. Nordstrom *et al*. [12] in their study including 5291 patients, found the PSAD cut-off value to be lower than similar studies (<0.07 ng/mL/cc). According to the authors, not performing a prostate biopsy in men with PSAD ≤0.07 ng/mL/cc would prevent 19.7% of patients from biopsy, while 6.9% of patients with csPCa would be missed [12]. Kosaka *et al*. [13] in their study, the PSAD cut-off value in predicting csPCa was found to be 0.032 ng/mL/cc. This cut-off value is slightly higher than the known value. The reason for this was thought to be that the study group of Kosaka *et al*.

Table 5. The distribution of Group 1 patients in quartiles when stratified by PSAD, total PSA, and PV

Parameter		<cut-off n (%)	>cut-off n (%)	P value
PSAD cut-off=0.157 ng/mL/cc	Total	95 (%56.5)	73 (%43.5)	**<0.001**
	Group 1	79 (%83.1)	36 (%49.3)	
	Group 2	16 (%16.9)	37 (%50.7)	
Total PSA cut-off=6.31 ng/mL	Total	82 (%48.8)	86 (%51.2)	**0.023**
	Group 1	63 (%76.8)	52 (%60.4)	
	Group 2	19 (%23.2)	34 (%29.6)	
Prostate Volume cut-off=35.5 cc	Total	61 (%36.3)	107 (%63.7)	**<0.001**
	Group 1	32 (%52.4)	83 (%77.5)	
	Group 2	29 (%47.6)	24 (%22.5)	

PSAD=Prostate-specific antigen density, PSA= Prostate-specific antigen, PV=Prostate volume, Group 1=clinically insignificant prostate cancer, Group 2= clinically significant prostate cancer

[13] consisted of patients under the age of 50. Although there is heterogeneity in the cut-off value of the studies, the cut-off value specified in the European Association of Urology guidelines is 0.1-0.15 ng/mL/cc [1]. In our study, the PSAD cut-off value was determined as 0.157 ng/mL/cc, in line with the guideline.

To overcome different cut-off values in PSAD, measuring prostate size by MRI can provide standardization. In the study performed by Distler *et al*. [14], it was stated that when MRI and PSAD were combined, the negative predictive value for csPCa increased from 79% to 89%.

The free/total PSA ratio is also an important PCa predictor. According to biopsy pathology results in men with serum PSA values in the range of 4-10 ng/mL, csPCa is detected in more than half of men with fPSA % <0.10. Gao *et al*. [15] evaluated 528 prostate cancer and 1127 BPH patients in their study and they determined a wider gray zone (2.5-25 ng/mL), contrary to what is known. According to the results, fPSA% was found to be the most effective predictor in patients with PSA values in this range, with an AUC value of 0.700 (cut-off value: 15.5%). [15]. In the study conducted by Shore *et al*. [16], the predictive effects of pro-PSA, total PSA, the prostate health index, and free PSA% were compared for PCa. fPSA% was found to be effective both in distinguishing PCa-BPH and in distinguishing between aggressive and non-aggressive PCa. However, the prostate health index was found to be superior to fPSA% in distinguishing between PCa and BPH. [16]. In this study, unlike the above studies, there was no statistically significant difference in fPSA% between the two groups.

The prostate volume provides important information for predicting malignant prostate diseases. However, data on its use in csPCa are limited. Erdogan *et al*. [17] found that the prostate volume in the patient groups with PSA levels of 2.5-10 ng/mL and 10-30 ng/mL was statistically significantly higher in the BPH group than in the PCa group. Chen *et al*. [18] stated in their study that lower rates of prostate cancer were detected in the patient group with larger prostate volume. Huang *et al*. [19] in their study investigated whether prostate volume has an additional predictive contribution to the prostate health index in the prediction of PCa. According to the results, they stated that prostate volume had no additional predictive value [19]. In the study we present, prostate volume was

found to be statistically significantly lower in the clinically significant prostate cancer group but was not found to be a predictive factor in multivariate analysis.

Limitations

First of the limitations of the study is that it was conducted with a small number of patients and a retrospective method. Another limitation is operator-induced differences in prostate volume measurement that may affect the PSAD value.

CONCLUSION

According to our results, PSAD plays an important role in predicting ciPCa. When deciding on biopsy, especially in patients with PSAD < 0.157 ng/mL/cc, benefiting from additional predictive factors will be beneficial to avoid overtreatment.

Ethical statement

This research was approved the University of Health Sciences Bursa Yuksek Ihtisas Training and Research Hospital ethics committee, dated 29.01.2020 and numbered 2020/01-08.

Authors' Contribution

Study Conception: SA, ÖE; Study Design: VÇ, AE; Supervision: EÖ, RÖ; Funding: UA, SÖ; Materials: SA, ÖE; Data Collection and/or Processing: VÇ, AE; Statistical Analysis and/or Data Interpretation: EÖ, RÖ; Literature Review: UA, SÖ; Manuscript Preparation: SA and Critical Review: SÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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